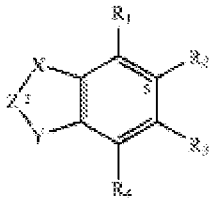
Claims Listing

1. (original) A method of inhibiting cytokine or biological activity of MIF comprising contacting MIF with a cytokine or biological activity inhibiting effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or prodrug thereof



(I)

wherein X is selected from —O—, —S—, —$C(R_5)(R_{5'})$— or —$N(R_6)$—; Y is selected from —$N(R_7)$—, —O—, —S— or —$C(R_7)_2$—; Z is selected from —C(O)—, —C(S)—, —$C(=NR_6)$—, —S(O)— or —$S(O)_2$—; R_1 is selected from hydrogen, $C_{1\text{-}3}$alkyl, $(CR_5R_{5'})_nOR_7$, $(CR_5R_{5'})_nSR_7$, $(CR_5R_{5'})_nN(R_6)_2$ and $(CR_5R_{5'})_n$halo; R_2 is selected from C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{12}R_{12'})_mC(O)R_8$, $(CR_{12}R_{12'})_mC(S)R_8$, $(CR_{12}R_{12'})_mS(O)R_8$, $(CR_{12}R_{12'})_mS(O)_2R_8$, $(CR_{12}R_{12'})_mOR_9$, $(CR_{12}R_{12'})_mSR_9$, $(CR_{12}R_{12'})_nNR_{10}R_{11}$, $(CR_{12}R_{12'})_mC(=NR_{24})R_{22}$ and $(CR_{12}R_{12'})_mR_{13}$; R_3 is selected from hydrogen, C_1-C_6alkyl, $(CR_{16}R_{16'})_pNR_{14}R_{15}$, $(CR_{16}R_{16'})_pOR_{17}$, $(CR_{16}R_{16'})_pSR_{17}$, $(CR_{16}R_{16'})_p$halo, $(CR_{16}R_{16'})_pNO_2$, $(CR_{16}R_{16'})_nC(O)R_{28}$, $(CR_{16}R_{16'})_nC(=NR_{24})R_{22}$, $(CR_{16}R_{16'})_nS(O)R_{17}$, $(CR_{16}R_{16'})_nS(O)_2R_{17}$, $(CR_{16}R_{16'})_nS(O)_3R_{17}$ and $(CR_{16}R_{16'})_pC(R_{18})_3$; R_4 is selected from hydrogen, halogen C_1-C_3alkyl, $C_{2\text{-}3}$alkenyl, $C_{2\text{-}3}$alkynyl and $(CR_{12}R_{2'})_nC(R_{18})_3$; Each R_5 and R_5 is independently selected from hydrogen, C_1-C_3alkyl, halo, OR_7, SR_7 and $N(R_6)_2$; Each R_6 is independently selected from hydrogen, C_1-C_3alkyl and OR_7; Each R_7 is independently selected from hydrogen and C_1-C_3alkyl; R_8 is selected from hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, OR_{19}, SR_{19}, $N(R_{20})_2$, $[NH—CH(R_{21})—C(O)]_q—OR_{29}$, $[sugar]_q$ and $(CR_{12}R_{12'})_tR_{13}$; R_9 is selected from hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl,

$(CR_{12}R_{12'})_tR_3$, $C(O)R_{23}$, CO_2R_{23}, $C(S)R_{23}$, $C(S)OR_{23}$, $S(O)R_{23}$, $S(O)_2R_{23}$, $[C(O)CH(R_{21})NH]_q$—R_{23} and $[sugar]_q$; R_{10} and R_{11} are independently selected from hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{12}R_{12'})_mR_{13}$, $C(O)R_{23}$, $C(S)R_{23}$, $S(O)R_{23}$, $S(O)_2R_{23}$, $[C(O)CH(R_{21})NH]_q$—R_{23}, -$[sugar]_q$ and $NHC(=NR_{25})$—NH_2; Each R_{12} and $R_{12'}$ is independently selected from hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, OR_{24}, SR_{24}, halo, $N(R_{24})_2$, CO_2R_{24}, CN, NO_2, aryl or heterocyclyl; R_{13} is selected from OR_{25}, SR_{25}, halo, $N(R_{25})_2$, $C(O)R_{31}$, CN, $C(R_{18})_3$, aryl or heterocyclyl; R_{14} and R_{15} are independently selected from hydrogen, C_1-C_3alkyl, OR_{17}, $(CR_{16}R_{16'})_pC(R_{18})_3$; Each R_{16} and R_{16} is independently selected from hydrogen, C_1-C_3alkyl, halo, OR_{17}, SR_{17} and $N(R_{17})_2$; Each R_{17} is independently selected from hydrogen and C_1-C_3alkyl; Each R_{18} is independently selected from hydrogen and halo; R_{19} and each R_{20} are independently selected from hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{26}R_{26'})_tR_{27}$; R_{21} is the characterising group of an amino acid; R_{22} is selected from C_1-C_6alkyl, NH_2, $NH(C_{1\text{-}6}alkyl)$, $N(C_{1\text{-}6}alkyl)_2$, OR_{29} or SR_{29}; R_{23} is selected from hydrogen, C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, aryl $(CR_{26}R_{26'})_tR_{27}$; Each R_{24} is independently selected from hydrogen and C_1-C_6alkyl; Each R_{25} is independently selected from hydrogen, C_1-C_6alkyl, $C_{1\text{-}3}$alkoxy$C_{1\text{-}3}$alkyl, aryl and heterocyclyl; Each R_{26} and $R_{26'}$ is independently selected from hydrogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, OR_{29}, SR_{29}, halo, $N(R_{29})_2$, CO_2R_{29}, CN, NO_2, aryl and heterocyclyl; R_{27} is selected from hydrogen, OR_{30}, SR_{30}, halo, $N(R_{30})_2$, CO_2R_{30}, aryl and heterocyclyl; R_{28} is selected from hydrogen, $C_{1\text{-}6}$alkyl, OR_{29}, SR_{29} or $N(R_{29})_2$; Each R_{29} is independently selected from hydrogen and C_1-C_3alkyl; Each R_{30} is independently selected from hydrogen, C_1-C_3alkyl, aryl and heterocyclyl; R_{31} is selected from $C_{1\text{-}3}$alkyl, OH, $C_{1\text{-}3}$alkoxy, aryl, aryloxy, heterocyclyl and heterocyclyloxy; n is 0 or an integer from 1 to 3; m is 0 or an integer from 1 to 20; p is 0 or an integer from 1 to 6; q is an integer from 1 to 5; t is an integer from 1 to

10; wherein alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

2. (original) A method according to claim 1 wherein X is selected from the group consisting of —N(H)—, —N(C_{1-3}alkyl)-, —N(OH)—, —N(OC_{1-3}alkyl)-, —O—, —S—, —CH_2, —CH(OH)—, —CH(NH_2)—, —CH(C_{1-3}alkyl)-, —CH(halo)-, —CH(SH)—, —CH(OC_{1-3}alkyl), —CH(SC_{1-3}alkyl)-.

3. (original) A method according to claim 1 wherein Y is selected from the group consisting of —NH—, —O—, —S—, —N(C_{1-3}alkyl)- or —CH_2—.

4. (original) A method according to claim 1 wherein Z is selected from the group consisting of —C(O)—, —C(S)—, —C(=NH)—, —C(=NC_{1-3}alkyl)-, —C(=NOH)— or —C(=NOC_{1-3}alkyl).

5. (original) A method according to claim 1 wherein R_1 is selected from the group consisting of hydrogen, CH_3, OH, SH, NH_2, $NHCH_3$, F, Cl or Br.

6. (original) A method according to claim 1 wherein R_2 is selected from the group consisting of C_{1-20}alkyl, C_{1-20}alkenyl, $(CR_{12}R_{12'})_m$heterocyclyl, $(CR_{12}R_{12'})_m$aryl, $(CR_{12}R_{12'})_m$halo, $(CR_{12}R_{12'})_m$OH, $(CR_{12}R_{12'})_m$OC_{1-20}alkyl, $(CR_{12}R_{12'})_m$OC_{2-20}alkenyl, $(CR_{12}R_{12'})_m$OC(O)C_{1-20}alkyl, $(CR_{12}R_{12'})_m$OC(O)C_{2-20}alkenyl, $(CR_{12}R_{12'})_m$OC(O)aryl, $(CR_{12}R_{12'})_m$O[C(O)CH(R_{21})NH]$_r$—H, $(CR_{12}R_{12'})_m$O[sugar]$_r$, $(CR_{12}R_{12'})_m$$NH_2$ $(CR_{12}R_{12'})_m$NHC_{1-20}alkyl, $(CR_{12}R_{12'})_m$N(C_{1-20}alkyl)$_2$, $(CR_{12}R_{12'})_m$NHC_{2-20}alkenyl, $(CR_{12}R_{12}—)_m$N(C_{2-20}alkenyl)$_2$, $(CR_{12}R_{12'})_m$N(C_{1-20}alkyl)(C_{2-}

$_{20}$alkenyl), $(CR_{12}R_{12'})_mNHC(O)C_{1-20}$alkyl, $(CR_{12}R_{12'})_mNHC(O)C_{2-20}$alkenyl, $(CR_{12}R_{12'})_nNHC(O)$aryl, $(CR_{12}R_{12'})_mNH[C(O)CH(R_{21})NH]_r$—H, $(CR_{12}R_{12'})_mNH$-[sugar]$_r$, $(CR_{12}R_{12'})_mSO_3H$, $(CR_{12}R_{12'})_mSO_3C_{1-20}$alkyl, $(CR_{12}R_{12'})_mSO_3C_{2-20}$alkenyl, $(CR_{12}R_{12'})_mC(O)C_{1-20}$alkyl, $(CR_{12}R_{12'})_mC(O)C_{2-20}$alkenyl, $(CR_{12}R_{12'})_mCO_2H$, $(CR_{12}R_{12'})_mCO_2C_{1-20}$alkyl, $(CR_{12}R_{12'})_mCO_2C_{2-20}$alkenyl, $(CR_{12}R_{12'})_mC(O)NHC_{1-20}$alkyl, $(CR_{12}R_{12'})_mC(O)N(C_{1-20}alkyl)_2$, $(CR_{12}R_{12'})_mC(O)NHC_{2-20}$alkenyl, $(CR_{12}R_{12'})_nC(O)N(C_{2-20}alkenyl)_2$, $(CR_{12}R_{12'})_mC(O)N(C_{1-20}$alkyl)($C_{2-20}$alkenyl), $(CR_{12}R_{12'})_mC(O)[NHCH(R_{21})C(O)]_r$—OH, $(CR_{12}R_{12'})_mC(O)[NHCH(R_{21})C(O)]_r$—$OCH_3$ $(CR_{12}R_{12'})_mC(O)$[sugar]$_r$, $(CR_{12}R_{12'})_mSC_{1-6}$alkyl, C(=N)$NHC_{1-6}$alkyl; wherein each R_{12} and $R_{12'}$ is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, halogen, OH, hydroxyC_{1-6}alkyl, OC_{1-6}alkyl, CO_2H, CO_2C_{1-3}alkyl, NH_2, NHC_{1-3}alkyl, $N(C_{1-3}alkyl)_2$, CN, NO_2, aryl or heterocyclyl; R_{21} is the characterising group of an amino acid, m is 0 or an integer from 1 to 20 and r is an integer from 1 to 5.

7. (original) A method according to claim 1 wherein R_3 is selected from the group consisting of hydrogen, halogen, C_1-C_6alkyl, —$(CH_2)_nNH_2$, —$(CH_2)_nNO_2$, —$(CH_2)_n$—OH, —$(CH_2)_n$—CF_3 or —$(CH_2)_n$—SH wherein n is as defined in claim 1.

8. (original) A method according to claim 1 wherein R_4 is selected from the group consisting of hydrogen, methyl, ethyl, —CH_2=CH_2, CH_2CF_3, fluoro, chloro or bromo.

9. (original) A method according to claim 1 wherein at least one of R_5 and $R_{5'}$ in each $(CR_5R_{5'})$ is hydrogen.

10. (original) A method according to claim 1 wherein at least one of R_{12} and R_{12}, in each ($CR_{12}R_{12'}$) is hydrogen.

11. (original) A method according to claim 1 wherein at least one of R_{16} and $R_{16'}$ in each ($CR_{16}R_{16'}$) is hydrogen.

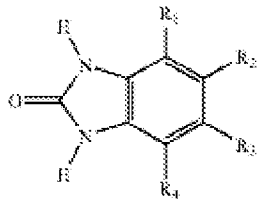
12. (original) A method according to claim 1 wherein at least one of R_{26} and $R_{26'}$ in each ($CR_{26}R_{26'}$) is hydrogen.

13. (original) A method according to claim 1 wherein X is selected from the group consisting of —O—, —S—, —$C(R_5)_2$— or —$N(R_6)$—; Y is selected from the group consisting of —$N(R_7)$—, —O—, —S—, or —$C(R_7)_2$—; Z is selected from the group consisting of —C(O)—, —C(S)—, —S(O)— or —C(=NR_6); R_1 is selected from the group consisting of hydrogen, CH_3, OH, SH, NH_2, $NHCH_3$, F, Cl or Br; R_2 is selected from the group consisting of C_1-C_{20}alkyl, C_2-C_{20}alkenyl, C_2-C_{20}alkynyl, $(CR_{12}R_{12'})_mC(O)R_8$, —$(CR_{12}R_{12'})_mC(S)R_8$, —$(CR_{12}R_{12'})_mS(O)R_8$, —$(CR_{12}R_{12'})_mS(O)_2R_8$, —$(CR_{12}R_{12'})_mOR_9$, —$(CR_{12}R_{12'})_mSR_9$, —$(CR_{12}R_{12'})_mNR_{10}R_{11}$, $(CR_{12}R_{12'})_mC(=NR_{24})R_{22}$ or $(CR_{12}R_{12'})_mR_{13}$ where m, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, $R_{12'}$, R_{13}, R_{22} and R_{24} are as defined in claim 1; R_3 is hydrogen, halogen, C_{1-6}alkyl, —$(CH_2)_nNH_2$, —$(CH_2)_nNO_2$, —$(CH_2)_n$—OH, —$(CH_2)_nCF_3$ or —$(CH_2)_nSH$ where n is as defined in claim 1; and R_4 is hydrogen, halogen, methyl, ethyl, CH_2CF_3 or —CH_2=CH_2.

14. (original) A method according to claim 1 wherein X is —$N(R_6)$—; Y is —$N(R_7)$— or —$C(R_7)_2$—; Z is —C(O)—, —C(S)—, —S(O)— or —C(=NH); R_1 is hydrogen,

CH_3, NH_2, $NHCH_3$, F, Cl or Br; R_2 is as defined in claim 1; R_3 is hydrogen, halogen, C_{1-3}alkyl, $(CH_2)_nNH_2$, —$(CH_2)_nNO_2$, $(CH_2)_nOH$ or $(CH_2)_nCF_3$ where n is defined in claim 1; and R_4 is hydrogen, halogen, methyl, ethyl, CH_2CF_3 or —CH_2═CH_2.

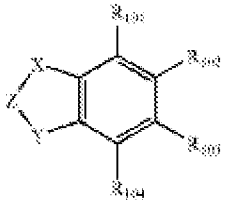
15. (original) A method according to claim 1 wherein the compound of formula (I) is a benzimidazole compounds having the formula (II):



(II)

wherein R_1 is hydrogen, CH_3, $NHCH_3$, F, Cl or Br; R_2 is as defined in claim 1; R_3 is hydrogen, halogen, C_1-C_3alkyl, $(CH_2)_nNH_2$, —$(CH_2)_nNO_2$, $(CH_2)_nOH$, $CH_2C(O)CH_3$, or $(CH_2)_nCF_3$ where n is as defined in claim 1; and R_4 is hydrogen, F, Cl or Br, methyl, ethyl, CH_2CF_3 or —CH_2═CH_2.

16. (original) A method according to claim 1 wherein the compound of formula (I) is a compound of formula (III):

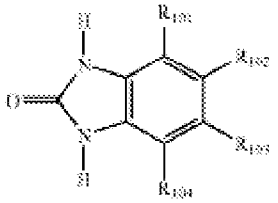


(III)

wherein X is —O—, —NH— or —CH_2—; Y is —NH—, —O—, —S— or —CH_2—; Z is —C(O)—, —C(S)— or —S(O)—; R_{10}, is selected from hydrogen, C_{1-3}alkyl, OH, SH, NH_2, NHC_{1-3}alkyl, F, Cl or Br; R_{102} is selected from C_{1-20}alkyl, C_{2-20}alkenyl, CO_2H, CO_2R_{105}, —NH_2, F, Cl,

Br, $(CH_2)_wR_{106}$, $C(O)N(R_{107})_2$, $C(=N)NHC_{1-6}$alkyl, SO_2C_{1-6}alkyl, $C(O)[NHCH(R_{108})C(O)]_q$—$OR_{109}$, C(O)sugar, $CONH(CH_2)_n$aryl, $NHC(O)(CH_2)_n$Sheterocyclyl, $C(O)SC_{1-6}$alkyl, $C(O)(CH_2)_nCO_2H$, SO_2OC_{1-10}alkyl, and SO_2NHC_{1-10}alkyl; R_{103} is selected from hydrogen, F, Cl, Br, C_1-alkyl, —$(CH_2)_nNH_2$, —$(CH_2)_nNO_2$, —(CH_2), —OH, —$(CH_2)_n$—CF_3, —$(CH_2)_nC(O)C_{1-3}$alkyl or —$(CH_2)_n$—SH; R_{104} is selected from hydrogen, methyl, ethyl, $CH_2C(R_{110})_3$, $C(R_{110})_3$, —CH_2=CH_2, fluoro, chloro or bromo; R_{105} is selected from hydrogen, C_{1-20}alkyl, C_{2-20}alkenyl or $(CH_2)_tOC_{1-3}$alkyl; R_{106} is selected from SH, SC_{1-6}alkyl, OH, OC_{1-6}alkyl, sugar, CO_2H, NH_2, heterocyclyl or aryl; Each R_{107} is independently selected from hydrogen, C_{1-20}alkyl, C_{2-20}alkenyl, $(CH_2)_t$aryl and $(CH_2)_t$heterocyclyl; R_{108} is the characterising group of an amino acid; R_{109} is hydrogen, C_{1-3}alkyl; Each R_{110} is independently selected from hydrogen and halo; and n is 0 or an integer from 1 to 3, q is an integer from 1 to 5, w is an integer from 1 to 6; t is an integer from 1 to 10; wherein each alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

17. (original) A method according to claim 1 wherein the compound of formula 1 is a compound of formula (IV):



(IV)

wherein R_{101} is selected from hydrogen, CH_3, OH, SH, NH_2, $NHCH_3$, F, Cl or Br; R_{102} is selected from C_{1-20}alkyl, C_{2-20}alkenyl, CO_2H, CO_2R_{105}, —NH_2, F, Cl, Br, $(CH_2)_wR_{106}$, $C(O)N(R_{107})_2$, $C(=N)NHC_{1-6}$alkyl, SO_2C_{1-6}alkyl, $C(O)[NHCH(R_{108})C(O)]_q$—$OR_{109}$, C(O)sugar,

$CONH(CH_2)_naryl$, $NHC(O)(CH_2)_nSheterocyclyl$, $C(O)SC_{1-6}alkyl$, $C(O)(CH_2)_nCO_2H$, $SO_2OC_{1-10}alkyl$, and $SO_2NHC_{1-10}alkyl$; R_{103} is selected from hydrogen, F, Cl, Br, $C_{1-6}alkyl$, $(CH_2)_nNH_2$, $—(CH_2)_nNO_2$, —(CH_2), —OH, $—(CH_2)_n—CF_3$, $CH_2C(O)CH_3$ or $—(CH_2)_n—SH$; R_{104} is selected from hydrogen, methyl, ethyl, CH_2CF_3, $—CH_2=CH_2$ fluoro, chloro or bromo; R_{105} is selected from hydrogen, $C_{1-10}alkyl$, $C_{2-10}alkenyl$, $(CH_2)_tOC_{1-3}alkyl$; R_{106} is selected from SH, $SC_{1-6}alkyl$, OH, $OC_{1-6}alkyl$, sugar, CO_2H, NH_2, heterocyclyl or aryl; Each R_{107} is independently selected from hydrogen, $C_{1-10}alkyl$, $C_{2-10}alkenyl$, $(CH_2)_taryl$ and $(CH_2)_theterocyclyl$; R_{108} is the characterising group of an amino acid; R_{109} is hydrogen, $C_{1-3}alkyl$; Each R_{110} is independently selected from hydrogen and halo; and n is 0 or an integer from 1 to 3, q is an integer from 1 to 5, w is an integer from 1 to 6, t is an integer from 1 to 10; wherein each alkyl, alkenyl, alkynyl, aryl and heterocyclyl may be optionally substituted.

18. (original) A method according to claim 1 wherein the compound of formula 1 is selected from the group consisting of: benzimidazole-2-one-5-n-pentanoate, 5-[2-(1-oxy-2-hydroxyethyl)ethyl]benzimidazol-2-one-5-carboxylate, benzimidazole-2-one-5-methanoate, benzimidazole-2-one-5-ethanoate, 3,4,5-tris(acetyloxy)-6-[(acetyloxy)methyl]tetrahydro-2H-pyran-2-yl-benzimidazole-2-one-5-carboxylate, 5-bromo-6-methylbenzimidazol-2-one, 5-hydroxy-6-methylbenzimidazol-2-one, 5-dodecanylbenzoimidazol-2-one, 4,5,7-tribromo-6-methylbenzimidazol-2-one, 4,5,6,7-tetrabromobenzimidazol-2-one, 5-methyl-6-nitrobenzimidazol-2-one, 5-amino-6-methylbenzimidazol-2-one, N-(6-methylbenzimidazol-5-yl)-2-pyrimidin-2-yl-sulfanyl-acetamide, pentyl-benzimidazol-2-one-5-carbothioate, 5-(benzimidazol-2(3H)-one-6-yl)-5-oxopentanoic acid, 2(3H)-benzimidazolone-5-sulfonic acid pentyl ester, 2(3H)-benzimidazolone-5-sulfonic acid pentyl amide, N-butyl-2-oxo-2,3-dihydro-

1H-1,3-benzimidazole-5-carboximidamide, 5-heptanoylbenzofuran-2(3H)-one, methyl 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoate, 3-hydroxy-2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}propanoic acid, methyl 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoate, 2-{[(2-oxo-2,3-dihydro-1H-1,3-benzimidazol-5-yl)carbonyl]amino}-3-phenyl propanoic acid, and N-(3,4-dihydroxyphenethyl)-2-oxo-2,3-dihydro-1H-1,3-benzimidazole-5-carboxamide.

19. (original) A method of treating, preventing or diagnosing a disease or condition wherein MIF cytokine or biological activity is implicated comprising the administration of a treatment, prevention or diagnostic effective amount of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof to a subject in need thereof.

20. (original) A method according to claim 19 wherein the disease or condition is selected from autoimmune diseases, solid or haemopoitic tumours and chronic or acute inflammatory diseases.

21. (original) A method according to claim 19 wherein the disease or condition is selected from the group consisting of Rheumatic diseases, spondyloarthropathies, crystal arthropathies, Lyme disease, connective tissue diseases, vasculitides, glomerulonephritis, interstitial nephritis, inflammatory bowel disease, peptic ulceration, gastritis, oesophagitis, liver disease, autoimmune diseases, pulmonary diseases, cancers whether primary or metastatic, atherosclerosis, disorders of the hypothalamic-pituitary-adrenal axis, brain disorders, corneal

disease, iritis, iridocyclitis, cataracts, uveitis, sarcoidosis, diseases characterised by modified angiogenesis, endometrial function, psoriasis, endotoxic (septic) shock, exotoxic (septic) shock, infective (true septic) shock, other complications of infection, pelvic inflammatory disease, transplant rejection, allergies, allergic rhinitis, bone diseases, atopic dermatitis, UV(B)-induced dermal cell activation, malarial complications, diabetes mellitus, pain, inflammatory consequences of trauma or ischaemia, testicular dysfunctions and wound healing.

22. (original) A method according to claim 21 wherein the disease or condition is selected from the group consisting of rheumatoid arthritis, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, reactive arthritis, Reiter's syndrome, gout, pseudogout, calcium pyrophosphate deposition disease, systemic lupus erythematosus, systemic sclerosis, polymyositis, dermatomyositis, Sjögren's syndrome, polyarteritis nodosa, Wegener's granulomatosis, Churg-Strauss syndrome, ulcerative colitis, Crohn's disease, cirrhosis, hepatitis, diabetes mellitus, thyroiditis, myasthenia gravis, sclerosing cholangitis, primary biliary cirrhosis, diffuse interstitial lung diseases, pneumoconioses, fibrosing alveolitis, asthma, bronchitis, bronchiectasis, chronic obstructive pulmonary disease, adult respiratory distress syndrome, colon cancer, lymphoma, lung cancer, melanoma, prostate cancer, breast cancer, stomach cancer, leukemia, cervical cancer and metastatic cancer, ischaemic heart disease, myocardial infarction, stroke, peripheral vascular disease, Alzheimer's disease, multiple sclerosis, diabetic retinopathy, parturition, endometriosis, osteoporosis, Paget's disease, sunburn and skin cancer.

23. (original) A method of claim 19 wherein the subject is a human subject.

24-25. (cancelled)

26. (original) A method of treating or preventing a disease or condition wherein MIF cytokine or biological activity is implicated comprising: administering to a mammal a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof and a second therapeutic agent.

27. (original) A method according to claim 26 wherein the second therapeutic agent is a glucocorticoid.

28. (original) A method of prophylaxis or treatment of a disease or condition for which treatment with a glucocorticoid is indicated, said method comprising: administering to a mammal a glucocorticoid and a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof.

29. (original) A method of treating a steroid-resistant disease or condition comprising: administering to a mammal a glucocorticoid and a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof.

30. (original) A method of enhancing the effect of a glucocorticoid in mammals comprising administering a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt or prodrug thereof simultaneously, separately or sequentially with said glucocorticoid.

31-40. (canceled)